III. REMARKS

Claim Status

Claims 1-2, 5, 7, 9-11 and 16-24 are active in the application and stand rejected. Claim 6 stands objected to.

Summary of Applicant's Invention

For the sake of completeness and integration, applicant repeats the short summary of his invention as presented in the last response.

Applicant's claims cover a oligonucleotide which is capable of binding to a telomerase protein. The oligonucleotide according to the invention is capable of binding to the telomerase simultaneously on two sites. It can bind to the template region of telomerase RNA and at the same time it is able of binding to the telomerase protein.

This dual binding is a very important feature of the invention. The dual binding is the reason why the oligonucleotide according to the invention is enormously effective, more than other inhibitors of telomerase in the state of the art.

At page 5, second fourth paragraph through page 6 first paragraph, applicant identifies the basis of the improved responses obtained by utilizing his novel oligomers.

> "According to the invention such chimeric oligonucleotides were prepared consisting of variously modified oligomeres optimized in view of the two targets and block, at the same time, the two enzyme binding sites of the telomeric

DNA. These two differently modified parts of the oligonucleotide are linked together.

They proved to be more efficient and selective than their individual components. In particular, chimeric oligonucleotides have proved to be successful, which are modified at the 5' end of the oligonucleotide by phosphorothioates, thus binding to the protein whereas being extended at the 3'end, e.g. by phosphoamidates or, if necessary, via a linker by PNAs thus concerning telomerase RNA. In this way selectivity and efficiency of phosphorothioate-modified oligonucleotides is increased essentially. In addition, we found that a further, remarkable increase in efficiency may be reached if the 3' end of the chimeric oligonucleotides according to the invention is modified by such nucleosides which additionally inhibit the catalytic centre of the enzyme (e.g. 3'azidodeoxyguanosine)."

Thus the novel oligonucleotides of claim 1 possess the novel and non-obvious capability of binding simultaneously to two sites of telomerase.

Applicants' discovery of these specific oligonucleotides and the use of such phosphorothioate-modified oligomers as a part of the chimeric oligonucleotides which are linked to a second oligonucleotide, binding tightly to the template region of telomerase RNA.

Only through the linkage of both oligomers in which each part contributes to the inhibition of telomerase activity can the high level of inhibition be obtained. The synergistic effect is what makes applicants composition the most effective inhibitor of telomerase.

Claim Rejections - 35 USC § 103

Claims 1-2, 5, 7, 9-11, 17-20, and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al. and Nielsen et al. (USP 5,539,082) in view of Norton et al. (1996) and Mata et al.

Applicant notes that in the immediately prior office action these same claims were rejected over Uhlmann et al. in view of Norton et al. (1996) and Mata et al. applicant believes the examiner's withdrawal of this rejection in favor of the new rejection is an implicit acknowledgement that applicant was persuasive in overcoming the prior rejection.

The examiner's rejoinder is that contrary to Applicant's assertions, the prior rejection was withdrawn in order to add the Nielsen et al. reference in order to strengthen the examiner's position. This acknowledgement is at minimum a suggestion that the examiner concluded that the prior rejection was insufficient as it stood. But this point has been discussed before and although applicant does not waive its argument on this point it is not fundamental to the issue of obviousness.

In applicant's last response with regard to the combination of Uhlmann et al. in view of Norton et al. (1996) and Mata et al. applicant stated:

> "It is noted that the combination of references do not teach that n is at least 10 and not more than 20, and p is at least 3 and not more than 17." [emphasis supplied]

The examiner has correctly summarized applicants argument at page 3 of the current office action by stating

> "Applicants concluded that Nielsen et al. does not cure the combination of the previously cited references. … Specifically, Applicants argued that the combined references do not teach that 'n is at least 10 and not more than 20, and p is at least 3 and not more than 17.' According to Applicants, at page 16 of the reply filed 5-30-08, the difference in the number of oligonucleotides cited in the prior art, in comparison to that set forth in the instant claims '*are the crux of applicant's invention.*' Applicants further argued that they reviewed Norton et al. and did not find an oligonucleotide of 15 nucleotides as suggested by the examiner. A full length copy of Norton et al. will be forwarded to Applicants; the table set forth on page 616 of this reference clearly sets forth telomerase binding oligonucleotides of at least 15 nucleotides in length.

Applicant thanks the examiner for transmitting the full length copy of Norton et al.

Norton et al. does disclose, as correctly stated by the examiner, a portion of the molecule instantly claimed by applicant, the PNA backbone of a protion of applicant's structure II. But the examiner does not refute the lack of disclosure of the other portion of applicant molecule as set forth in the underlined extract from the office action.

Nowhere do the references, even if combined, show a molecule where "n is at least 10 and not more than 20, and p [z] is at least 3 and not more than 17". Norton et al. may well disclose "n" but clearly do not show "p [z] is at least 3 and not more than 17". Nor do the other references, alone or in combination.

The examiner states that "Norton et al. discloses the nucleotide structure of an oligomer (15 base pairs in length;

i.e. satisfying n and p)" but disregards the structure of the molecules set forth in applicants claims and Norton et al.

Applicant's claims indisputably show a structure distinctly different from that of Norton et al.'s Figure 1 on page 615. the "n" portion of applicants molecule is different from the "p" portion. Adding the same 15 base pairs in length backbone of Norton et al. does not satisfy applicant's structures I, II or III in that the "n" portion of applicants molecule differs from the "p" portion of applicants molecule. All of Norton et al.'s backbone consists of repeating N-(2-aminoethyl)-glycine units while none of applicant's structure I or III does; in applicants structure II only the "z" portion has repeating N-(2-aminoethyl)-glycine units.

As stated by the examiner, "arguments of counsel may be effective in establishing that an examiner has not properly met his or her burden or has otherwise erred in his or her position. However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure."

Applicant again respectfully would request the examiner to review the previously submitted Declaration of Dr. Eckhart Matthes where the functionality of applicants molecules is fully explicated. At paragraph 6, Dr. Matthes indicates that the finding reported in the therein cited paper is key to understanding the possibly of linking two ODN's and providing dual linking. At paragraph 10, Dr. Matthes states his professional disagreement with the examiner's conclusion and explicates his rationale in the following paragraphs, in

particular paragraph 17 and 18. Further, paragraph 20 highlights that the conclusions of Dr. Matthes were surprising to one skilled in the art.

Applicants disclose using antisense ODN (with different modifications, including PNA) to reach the template site of telomerase RNA but, as described, applicants have linked them to second oligomers able to bind additionally to the telomerase protein.

Thus, two telomerase targets can be reached by applicants chimeric ODN: the primer binding site of the protein and the template region of RNA.

ODN which hit two targets of telomerase as do applicants chimeric ODN have never been described before and are not described by Nielsen et al.

For the examiner's ease in reconsideration of this ground for rejection applicant repeats, in the following, the points made in response to the last office action regarding this ground for rejection.

Uhlmann et al. teach the synthesis and properties of PNA and DNA chimeras of any desired sequence by an automated synthesizer and in one particular embodiment, disclose compounds of the following structure:

5'-GGGACCAtggcagcc-h where h is HN-$(CH_2)_6$-OH

which corresponds to nucleotides having oligomers on the 3' end of the structure comprising a terminal amino group having an acid labile protecting group.

However, as recognized by the examiner, Uhlmann et al. does not teach wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17. Moreover, Uhlmann et al. does not teach wherein this structure inhibits the activity of telomerase, or wherein the chimeric oligonucleotide structure comprises a terminal amino group.

Norton et al. is cited by the examiner as teaching the inhibition of human telomerase activity by peptide nucleic acids (PNAs). According to Norton et al. PNAs recognize the RNA component of human telomerase (hTR) and inhibit activity of the enzyme. Inhibition depends on targeting exact functional boundaries of the hTR template. Norton et al. also observed that phosphorothioate (PS) oligomers inhibit telomerase in a non-sequence selective fashion.

Additionally, Mata et al. is cited by the examiner as teaching that hexameric phosphorothioate oligomers function to inhibit telomerase activity and arrests growth of Burkitts lymphoma cells.

The examiner concludes that it would have been obvious to the ordinary skilled artisan to combine the teachings of the above-cited references in the design of the present invention and that one of ordinary skill in the art would have been motivated to make the oligomers of the present invention to comprise wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17, since Uhlmann et al. clearly teach that chimeric PNA/DNA oligonucleotides or any sequence can be readily prepared.

The examiner also states that Norton et al. discloses the nucleotide structure of an oligomer 15 base pairs in length. But this disclosure would not lead one skilled in the art to an appreciation of the number of units of "n" and the number of units of "p" [now "z"] that are the crux of applicant's invention.

So all that is disclosed is a different composition that may by chemical manipulation be changed into the claimed compound, but without any understanding or motivation as to the benefit of the manipulation step.

As stated above Nielsen et al. do not cure the deficiencies in the examiner's argument.

Applicant believes a *prima facie* case has not been made by the examiner and therefore requests favorable reconsideration of this ground for rejection.

As an additional ground for positive reconsideration of claim 5, applicant notes that claim 5 requires that the nucleotides vary one from another and that is not disclosed in Nielsen et al., where adjacent nucleotides are repeated.

Conclusion

Based on the foregoing remarks it is believed that the claim is in condition for allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved. If any extension of time for this response is required, Applicants

request that this be considered a petition therefore. Please charge any insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

Respectfully submitted,

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